# From Post-Viral Arthritis to Post-Viral Syndrome: Immunologic Hypotheses

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# Disclosures

The following presentation as prepared by the presenter (HA) in her personal capacity. The opinions expressed in it are her own and do not reflect the view of the Food and Drug Administration, the Department of Health and Human Services, or the U.S. Government.

Post-viral syndromes are an area of actively evolving research, in which scientific consensus and clinical standards of care are still emerging. Owing to the nature of the topic, much of the information in this presentation is investigational and exploratory. The presenter acknowledges and takes responsibility for the limitations of the information presented.

The presenter acknowledges and gives thanks for the contributions of people with lived experience to the study of post-viral conditions.

# Agenda

1. Audience Polls
2. Post-Viral Arthritis: (more) Chikungunya
3. Post-Viral Definitions & Challenges: PASC
4. Immunologic Clues and Hypotheses
5. Discussion

# Audience Poll

# Question 1:

There is currently a clear scientific consensus in my field about how to manage post-viral inflammatory or immunologic phenomena.

A – disagree strongly

B – disagree slightly

C – neither agree nor disagree

D – agree slightly

E – agree strongly

# Question 2:

I feel confident about managing patients with prolonged post-viral arthritis and related symptoms.

A – disagree strongly

B – disagree slightly

C – neither agree nor disagree

D – agree slightly

E – agree strongly

# Question 2:

Compared to 5 years ago, I am now seeing _____ patients referred for prolonged symptoms or abnormal laboratory findings following a viral infection.

A – much fewer

B – slightly fewer

C – about the same

D – slightly more

E – much more

# Chikungunya Arthritis

# Chikungunya: Viral and Post-Viral Arthritis

- Revisit: Polyarticular arthralgias feature prominently in acute infection with CHIKV, can persist for months; chronic in 25% of some cohorts.
  - Other alphaviruses associated with severe arthritis: Mayaro, Ross River, O'nyong'nyong
- Mechanism: virus persistence, molecular mimicry, or dysregulated adaptive immune response? Some clues
- Large number of $T_{eff}$ cells infiltrate synovium in CHIKV arthritis
- Lack of $T_{reg}$ activity associated with CHIKV arthritis in some studies
- Does an imbalance of $T_{eff}/T_{reg}$ activity result in dysregulated inflammatory processes that contribute to tissue damage and symptoms?

PMID 29266783, 18611153, 23209328, 28840350, 30347791, 36275717

# Chikungunya Arthritis: Cytokines and T-cells

- Study aimed to define the relationship between chronic CHIKV post-viral arthritis disease severity, cytokine response and T cell subsets in order to identify potential targets for therapy.
- Participants with >3 months of post-CHIKV arthritis recruited in Colombia in 2019-2021. Original case-control design was modified to case-only due to COVID-19 pandemic.
- Arthritis severity was quantified using the Disease Activity Score-28 and an Arthritis-Flare Questionnaire adapted for chikungunya arthritis.
- Plasma cytokine concentrations (interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, interferon-γ and tumor necrosis factor (TNF)) were measured using a Meso Scale Diagnostics assay. Peripheral blood T cell subsets were measured using flow cytometry.

Chang AY, Tritsch SR, Herrera Gomez CA, et al. (2024) Cytokine and T cell responses in post-chikungunya viral arthritis: A cross-sectional study. PLoS ONE 19(3): e0299521. PMID 38507338.

# Chikungunya Arthritis: Cytokines and T-cells

- 175 participants with clinical CHIKV infection >3 months prior were enrolled between November 2019 and August 2021. 17 were excluded due to lack of serologic confirmation.
- Among 158 evaluable participants, median age was 48.6 (SD =15.9) and 127 (80%) were female.
- All participants self-identified as the Colombian mestizo ethnicity (i.e., mixed European, often Iberian, and indigenous Latin American ancestry).
- Disease Activity Scores (DAS-28) ranged from 0.96 (remission) to 6.48 (severe arthritis activity). Participants reported moderate disease activity on average, DAS-28 mean of 3.66 (SD = 1.23).
- When DAS-28 results were stratified by demographics, older participants showed a trend towards greater disease activity ($p = 0.07$) and female sex was associated with more active arthritis ($p = 0.03$). Educational level was not related to disease activity.
- Most commonly reported medical therapies were acetaminophen (90.2%; most in remission), ibuprofen (74.0%; lower symptoms burden), and steroids (33%; highest symptoms burden).

Chang 2024, PMID 38507338.

# Chikungunya Arthritis: Cytokines and T-cells

**Table 4. Causes of arthritis flares in chikungunya arthritis cases grouped by disease activity Score-28 compared using Kruskal-Wallis analysis.**

| Cause | All Cases | Remission 0–2.6 | Mild 2.6–3.2 | Moderate 3.2–5.1 | Severe 5.1+ | H (df = 1) | P |
|---|---|---|---|---|---|---|---|
| **Exercise** | 42% (66/158) | 32% (9/28) | 24% (5/21) | 50% (46/92) | 35% (6/17) | 1.27 | 0.26 |
| **Infection** | 18% (29/158) | 7% (2/28) | 14% (3/21) | 22% (20/92) | 24% (4/17) | 5.89 | 0.02 |
| **Food** | 4% (6/158) | 0% (0/28) | 5% (1/21) | 5% (5/92) | 0% (0/17) | 0.07 | 0.79 |
| **Medications** | 1% (1/158) | 0% (0/28) | 0% (0/21) | 1% (1/92) | 0% (0/17) | 0.05 | 0.82 |
| **Other factor** | 16% (25/158) | 14% (4/28) | 29% (6/21) | 15% (14/92) | 6% (1/17) | 2.39 | 0.12 |

- Exercise (42%) and a recent infection (18%) were most commonly associated with arthritis flares.
- Participants with increasing arthritis severity were more likely to report recent infection as a cause of flare ($H(1) = 5.89, P = 0.02$).
- A few participants reported specific foods or new medications as inciting factors for arthritis flares.
- Other factors reported including exposure to cold temperatures.

Chang 2024, PMID 38507338.

# Chikungunya Arthritis: Cytokines and T-cells

- Among participants with post-CHIKV arthritis, CRP levels correlated with both DAS-28 arthritis disease activity ($p = <0.001$) and increased flare severity ($p = 0.03$).
- Increased arthritis disease activity was associated with higher levels of inflammatory cytokines, including IL-6 ($p = 0.03$) and TNF ($p = 0.009$) and immunoregulatory cytokine IL-10 ($p = 0.03$).
- Levels of IL-1β, IL-2, IL-4, IL-8, IL-12p70, IL-13 and interferon-γ were not correlated with disease severity by DAS-28 or flare score.
- Increased arthritis disease flare activity was associated with higher levels of $T_{reg}$ ($p = 0.03$).
- Higher IL-2 levels correlated with increased $T_{reg}$ counts ($p = 0.03$), $\%T_{reg}$ ($p = 0.01$), and immunosuppressive $T_{reg}$ markers.
- Higher IL-2 was also associated with increased $\%T_{eff}$ ($p = 0.008$).

Chang 2024, PMID 38507338.

**Table 6. Associations of T cell subsets with IL-2 level in chikungunya arthritis cases.**

| T cell subset | Spearman correlation ($r_s$) | P value |
|---|---|---|
| Teff count | 0.14 | 0.07 |
| % Teff /Live lymphocytes | 0.21 | 0.008 |
| % Teff/CD4$^+$ T cells | 0.12 | 0.13 |
| Treg count | 0.17 | 0.03 |
| %Treg/Live lymphocytes | 0.15 | 0.053 |
| % Treg/CD4$^+$ T cells | 0.20 | 0.01 |
| Tregs CTLA4$^+$ | 0.27 | <0.001 |
| Tregs Helios | 0.17 | 0.03 |
| Tregs HLADR | 0.18 | 0.03 |
| Tregs CCR7 | -0.21 | 0.007 |
| Tregs CD45RA | 0.18* | 0.02 |

# Chikungunya Arthritis: Cytokines and T-cells

- Key finding: post-CHIKV arthritis disease activity was associated with increased inflammatory cytokines and IL-10 immunoregulatory cytokine concentrations.
- IL-2 levels in this post-CHIKV arthritis cohort were low in comparison to those reported in healthy adults and patients with RA. Higher IL-2 levels correlated with increased $T_{reg}$ number and functional markers, but also increased $\%T_{eff}$.
- "The lack of IL-2 and $T_{reg}$ in post-CHIKV arthritis may result from prolonged exposure to the CHIKV viral antigens that drive differentiation of naïve T cells into $T_{eff}$ as opposed to $T_{reg}$. This hypothesis is consistent with our [prior] findings that ≥4 days of initial viral symptoms was a significant predictor of persistent joint pain and with our [new] finding that longer days of initial fever were associated with higher subsequent arthritis severity.
- Study conclusion: further study into IL-2 pathway for therapies may be warranted.

Chang 2024, PMID 38507338.

# T-cells in Alphavirus and Flavivirus Infections

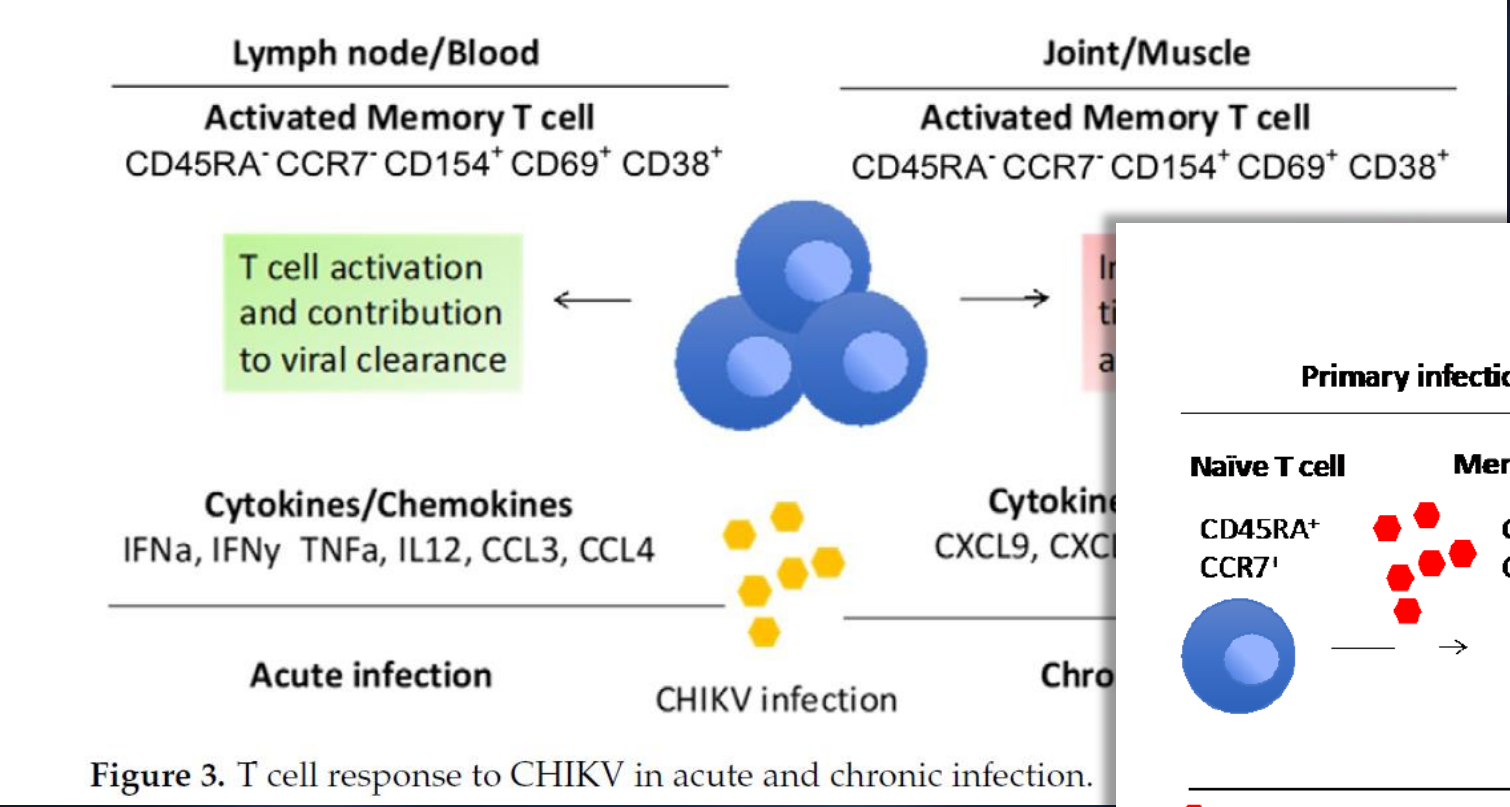



Figure 3. T cell response to CHIKV in acute and chronic infection.

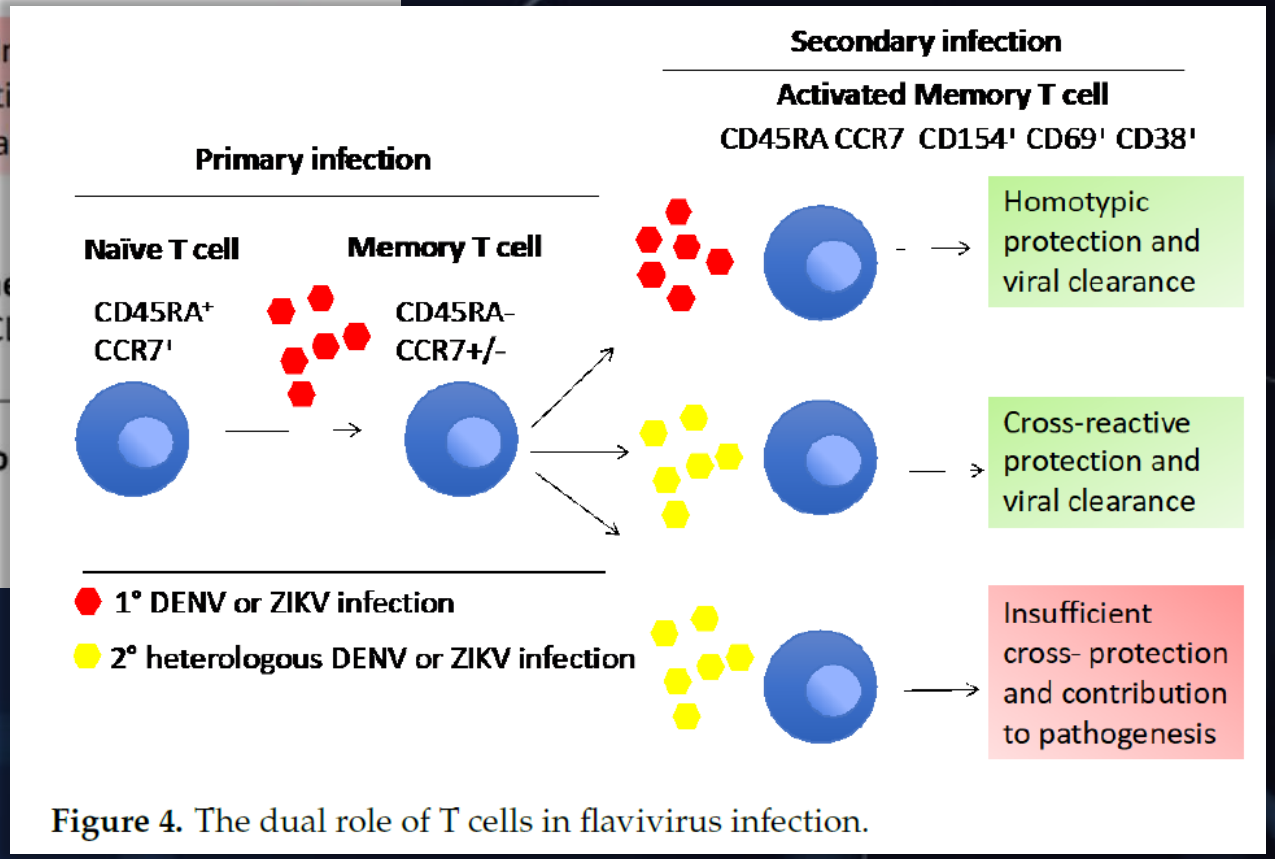
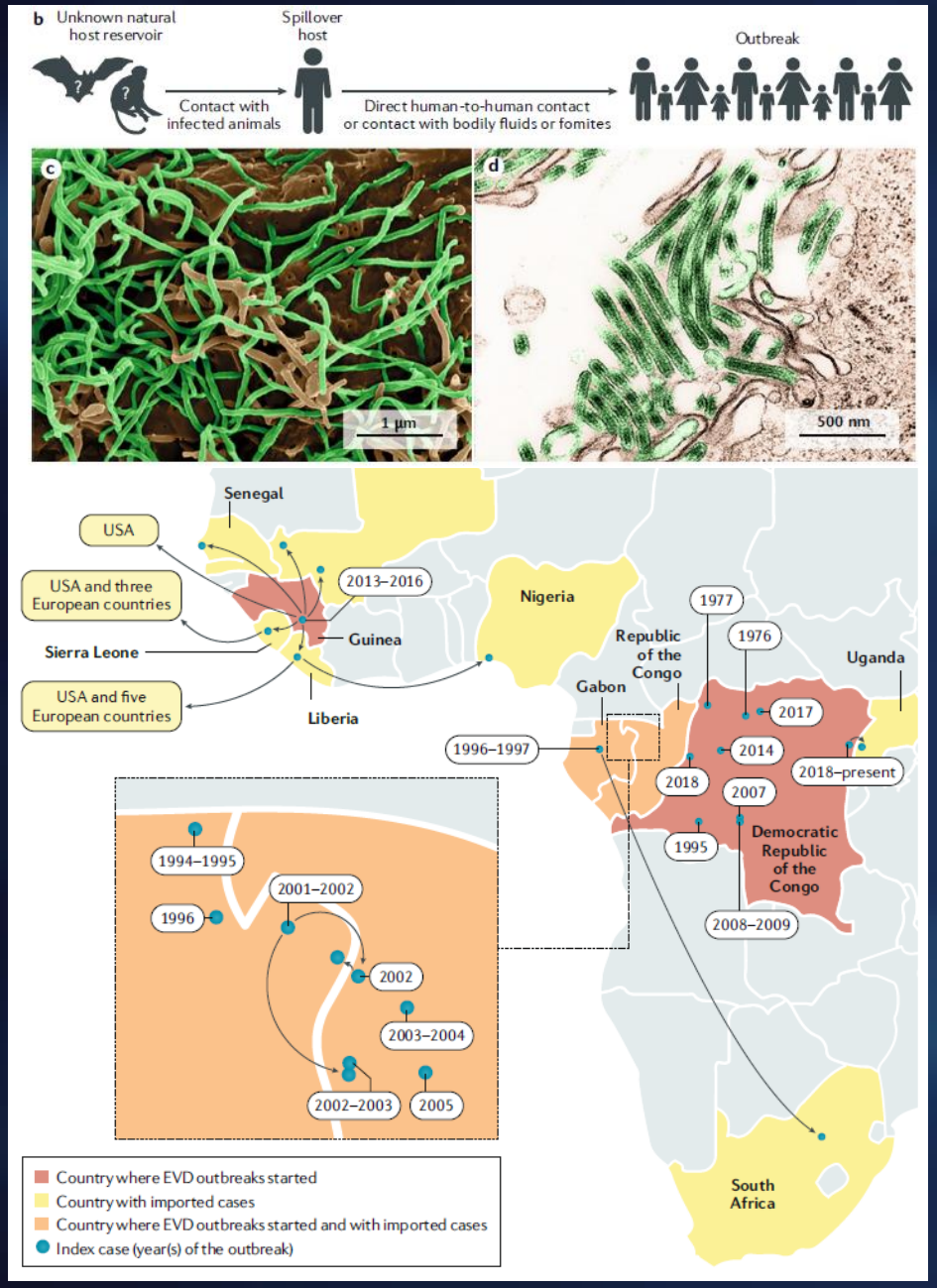
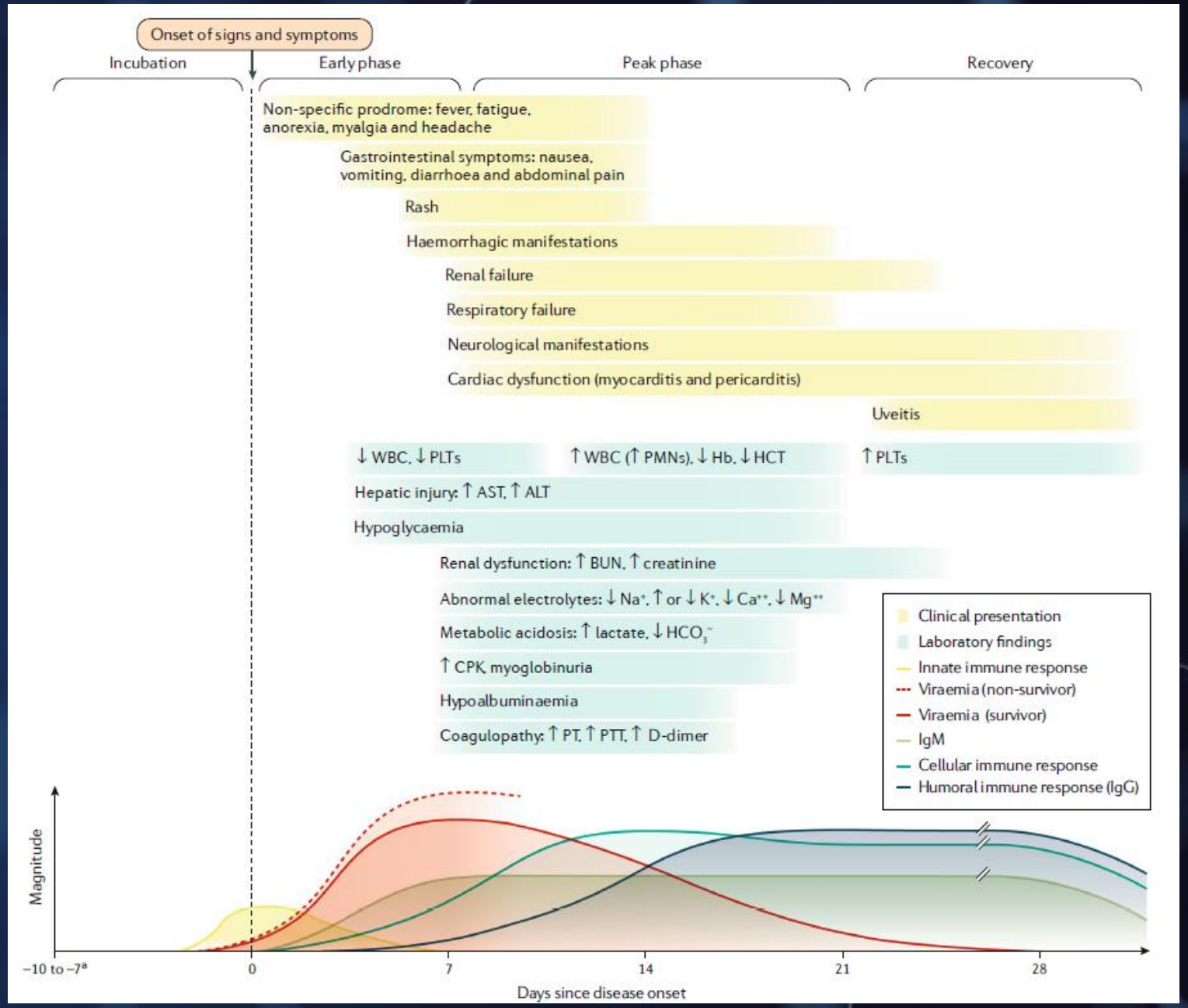



Figure 4. The dual role of T cells in flavivirus infection.

Mapalgamage 2022, PMID 35215836

# A Different Virus




Jacobs, Crozier et al. ,2020, PMID 32080199

**Generalized, non-specific manifestations**
- Fatigue[a]
- Weight gain, anorexia, fever, chills, night sweats and lymphadenopathy[b]
- Anaemia[c]

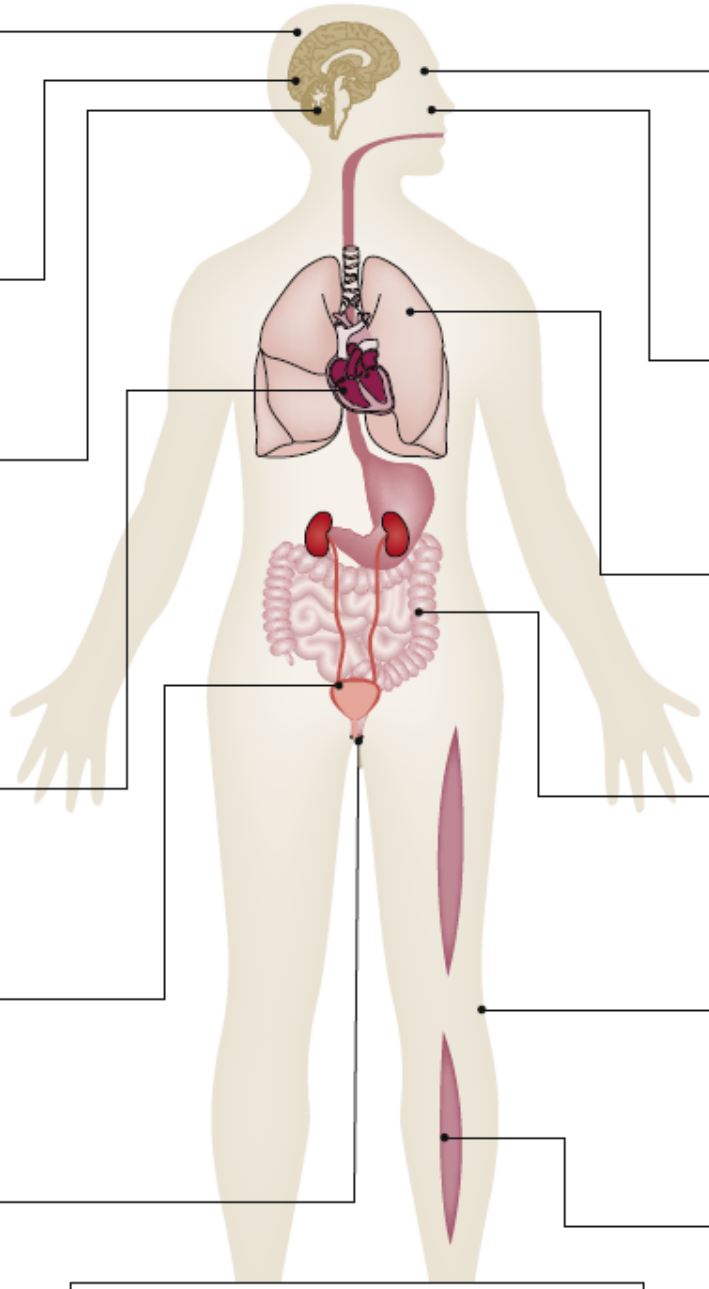
**Psychosocial and/or mental health issues**
- Insomnia[b]
- Anxiety disorders, depression and PTSD[c]

**Central or peripheral nervous system**
- Abnormal neurological examination[a,d], headache[a] and memory loss[a]
- Dizziness, paraesthesia, diplopia, vertigo, ataxia, limb weakness and tremor[b]
- ○ Meningoencephalitis[c]
- Seizures[c] and cerebrovascular accident[c]

**Cardiovascular system**
- Abnormal cardiovascular examination[a,e]
- Palpitations, chest pain and cardiogenic oedema[b]

**Urinary tract**
- Urinary frequency[a]
- Urinary urgency, nocturia, dysuria, polyuria and incontinence[b]

**Reproductive system**
- Male: impotence and/or decreased libido and orchitis[b]
- Female: decreased libido, amenorrhoea, abnormal odour and abnormal vaginal bleeding[b]



○ Linked to EBOV persistence leading to organ-specific inflammation

**Eye and/or vision**
- ○ Uveitis[a]
- Loss of vision and diplopia[b]
- Cataract, blurry vision, light sensitivity, itchy eye, tearing, eye pain, burning, redness, dryness, foreign body sensation, floaters and photopsia[c]

**Head, ears, nose and throat**
- Hearing loss; tinnitus; ear, nose or throat pain; and hoarseness[b]
- Aural fullness[c]

**Respiratory system**
- Shortness of breath, cough and/or sputum production, paroxysmal nocturnal dyspnoea and wheezing[b]

**Gastrointestinal system**
- Abnormal abdominal examination[a,f]
- Abdominal pain, nausea, change in bowel habits, melaena and diarrhoea[b]

**Skin**
- Itching and hair changes, with or without nail changes[b]
- Alopecia[c]

**Musculoskeletal system**
- Abnormal musculoskeletal examination[a,g], arthralgia[a] and myalgia[a]
- Joint or muscle stiffness, warmth or effusion[b]

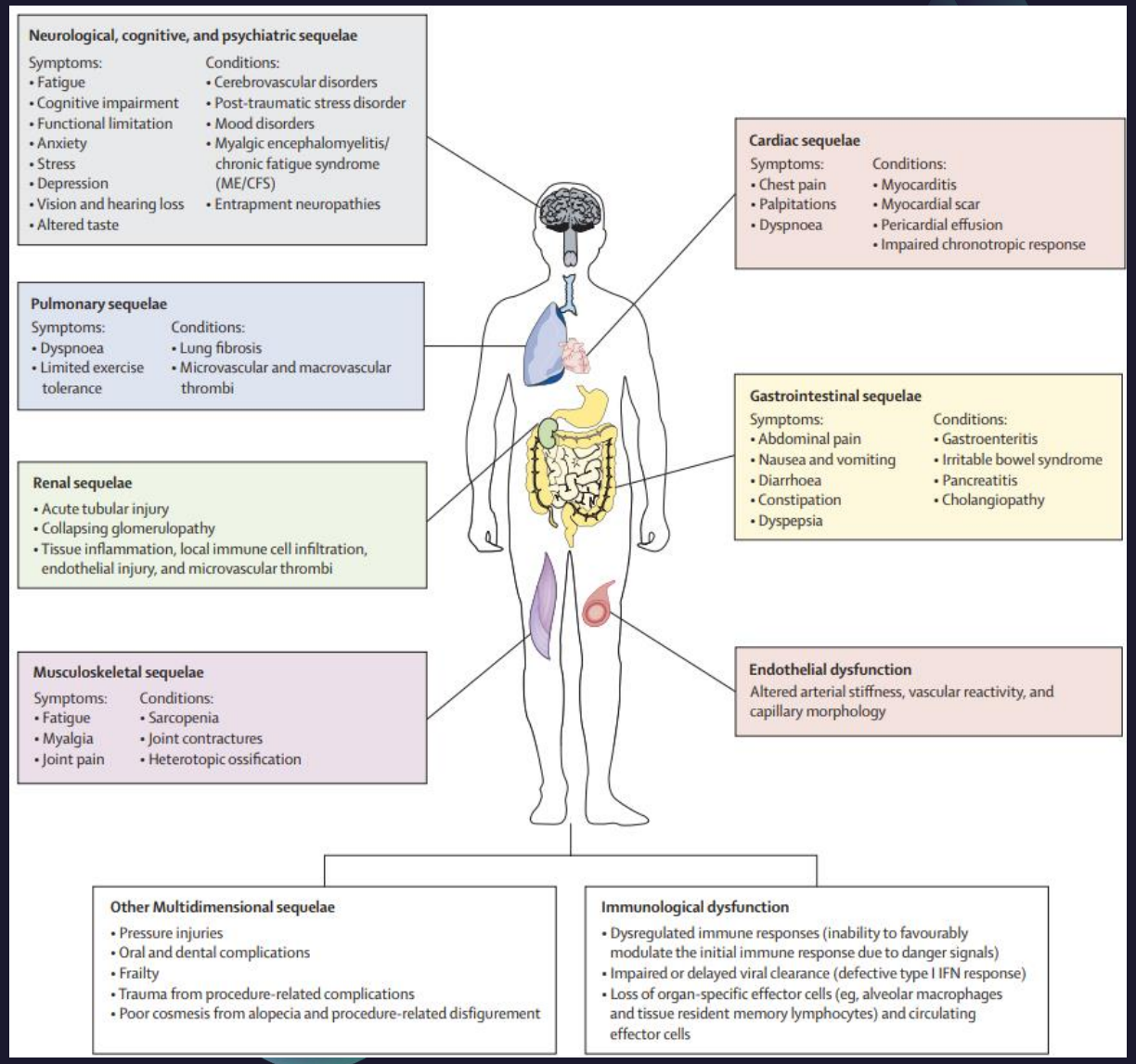
PMID 32080199

# Post-Acute Sequelae of COVID-19 (PASC)

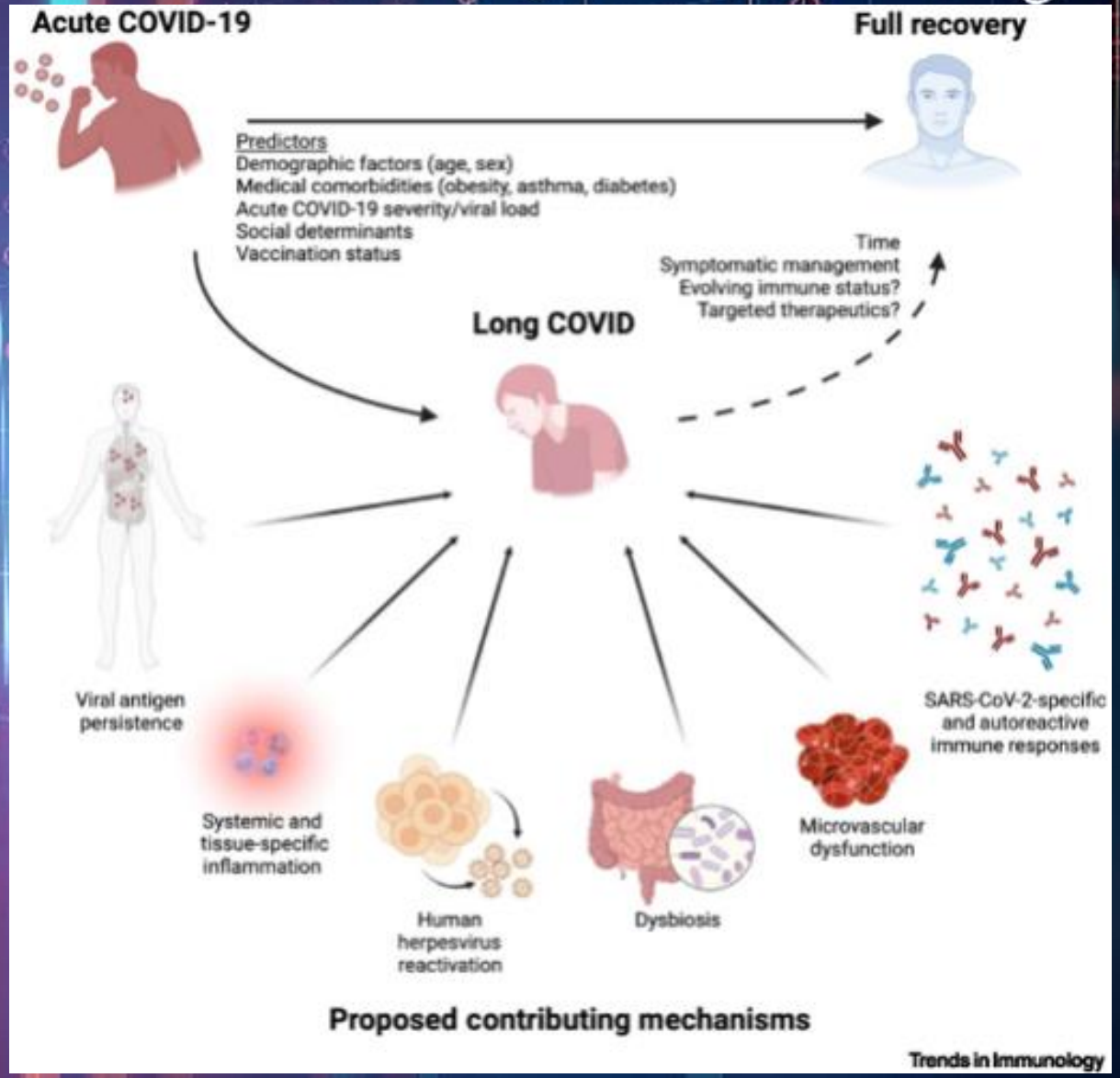
# PASC a.k.a. Post-COVID Condition a.k.a. Long COVID

- WHO (2022): Persistent or newly developed symptoms ≥3 months after initial SARS-CoV-2 infection, which last for ≥ 2 months with no other explanation.
- CDC and DHHS (2024): Broadly defined as "new, returning, or ongoing health problems people can experience four or more weeks after initial infection with the SARS-CoV-2."
- Estimated to affect 5-20% of people after COVID-19; estimates have varied with definition, reporting method, population, SARS-CoV-2 variant, and vaccination status.
- Per latest CDC Pulse survey (March 2024), 17% of US adults have ever had Long COVID and 7% are currently experiencing symptoms; of these, 25% report significant activity limitations.

Post COVID-19 condition (Long COVID) (who.int) The Office of Long COVID Research and Practice (OLC) | HHS.gov
Terms & Definitions | COVID.gov Long COVID - Household Pulse Survey - COVID-19 (cdc.gov)




Parotto 2023, PIMD 37475125



Original Investigation FREE

May 25, 2023

# Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD[1,2]; Sarah E. Jolley, MD, MS[3]; Elizabeth W. Karlson, MD, MS[4]; et al

» Author Affiliations | Article Information

*JAMA*. 2023;329(22):1934-1946. doi:10.1001/jama.2023.8823

- RECOVER prospective observational cohort study of adults with and without SARS-CoV-2 infection at 85 enrolling sites (hospitals, health centers, community organizations) located in 33 states, Washington, DC, and Puerto Rico.
- Participants completed a symptom survey ≥6 months after acute symptom onset or test date.
- 9,764 participants (89% SARS-CoV-2 infected; 71% female; 16% Hispanic/Latino; 15% non-Hispanic Black; median age, 47 years.

Thaweethai et al., 2023, PMID 37278994

- aOR (infected vs uninfected participants) were 1.5 or greater for 37 symptoms.
- Symptoms contributing to PASC score included postexertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, palpitations, changes in sexual desire or capacity, loss of or change in smell or taste, thirst, chronic cough, chest pain, and abnormal movements.
- Among 2,231 participants first infected on or after December 1, 2021, and enrolled within 30 days of infection, 224 (10% [95% CI, 8.8%-11%]) were PASC positive at 6 months.

**eTable 10. PASC onset and resolution over time**

| 6-month PASC Status | 9-month PASC Status | | Total[a] |
|---|---|---|---|
| | Unspecified | PASC-positive | |
| Unspecified | 2199 (93.3%) | 158 (6.7%) | 2,357 |
| PASC-positive | 133 (32.5%) | 276 (67.5%) | 409 |
| Total | 2332 (84.3%) | 434 (15.7%) | 2,766 |

[a]Inclusive of acute and postacute cohort participants who completed both 6- and 9-month visits.

Original Investigation FREE

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Table 2.

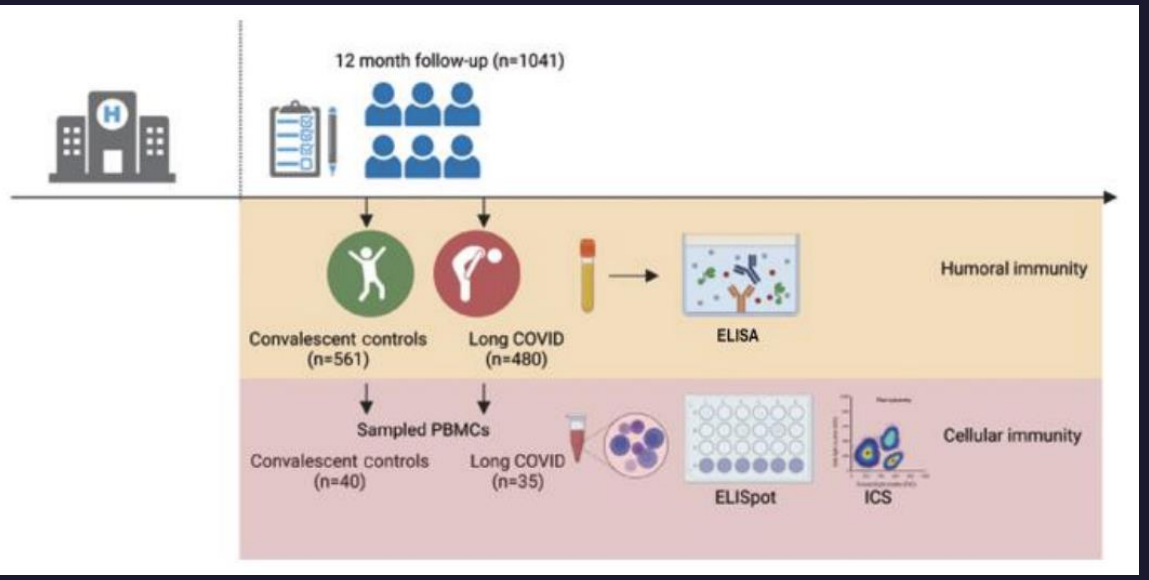
**Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]**

| Symptom | Log odds ratio | Score |
|---|---|---|
| Smell/taste | 0.776 | 8 |
| Postexertional malaise | 0.674 | 7 |
| Chronic cough | 0.438 | 4 |
| Brain fog[b] | 0.325 | 3 |
| Thirst | 0.255 | 3 |
| Palpitations | 0.238 | 2 |
| Chest pain[b] | 0.233 | 2 |
| Fatigue[b] | 0.148 | 1 |
| Sexual desire or capacity | 0.126 | 1 |
| Dizzines | 0.121 | 1 |
| Gastrointestinal | 0.085 | 1 |
| Abnormal movements | 0.072 | 1 |
| Hair loss | 0.049 | 0 |

Abbreviation: PASC, postacute sequelae of SARS-CoV-2 infection.

*Open Forum Infectious Diseases*
MAJOR ARTICLE
IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

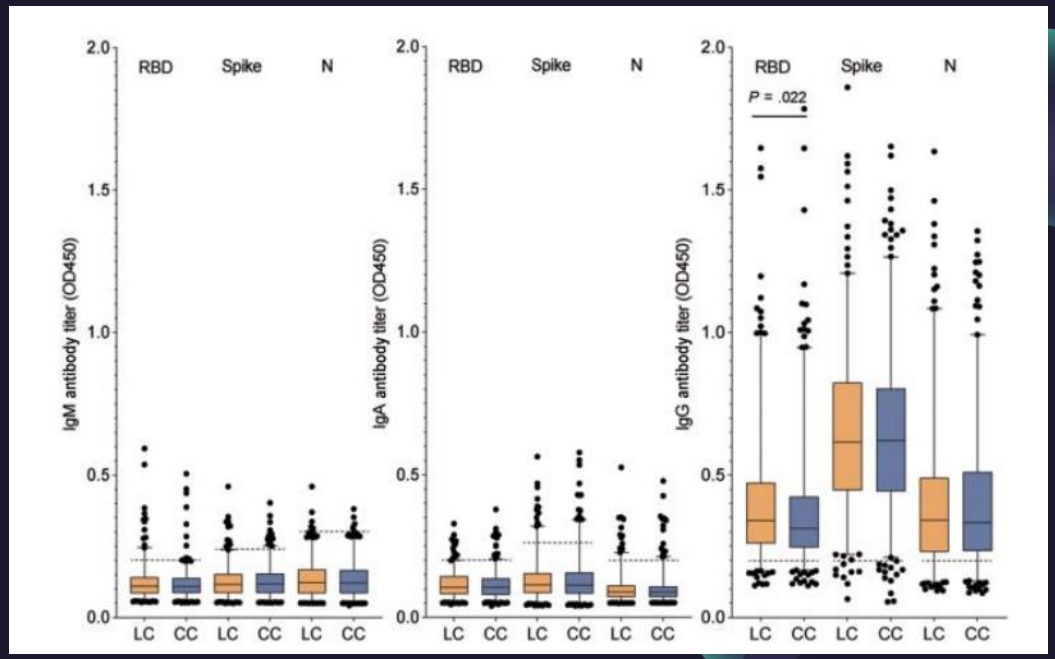
# Immune Responses in Discharged COVID-19 Patients With and Without Long COVID Symptoms



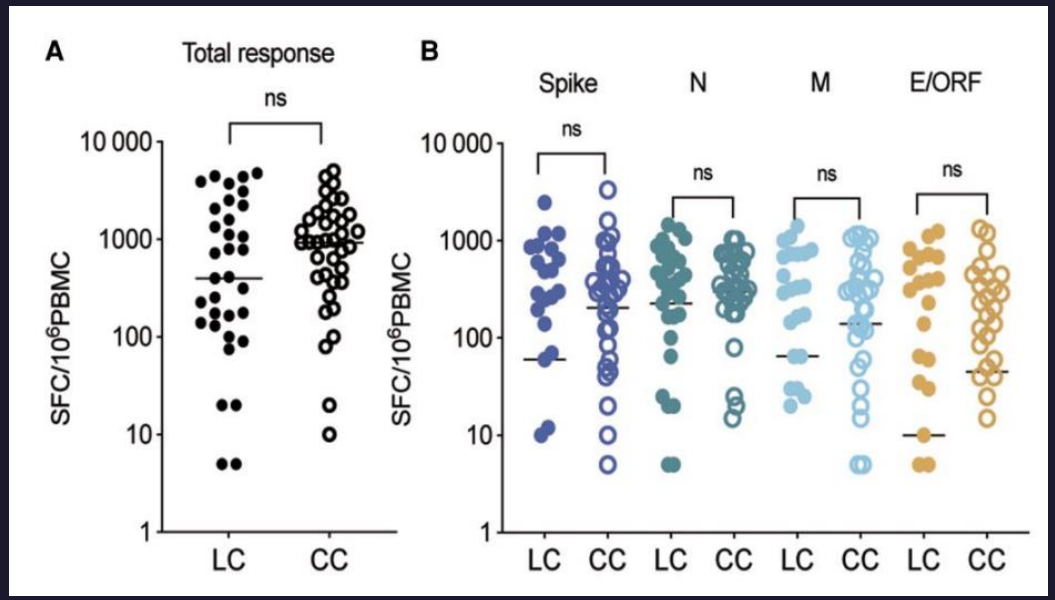

- 1041 patients hospitalized with COVID-19 (original strain) in Wuhan, assessed at 12 months
- Found higher levels of RBD-IgG antibodies in LC compared to CC, however no corresponding difference in T-cell immunity

Wang 2024, PMID 38577029

SARS-CoV2-specific Antibodies




SARS-CoV2-specific T-Cells

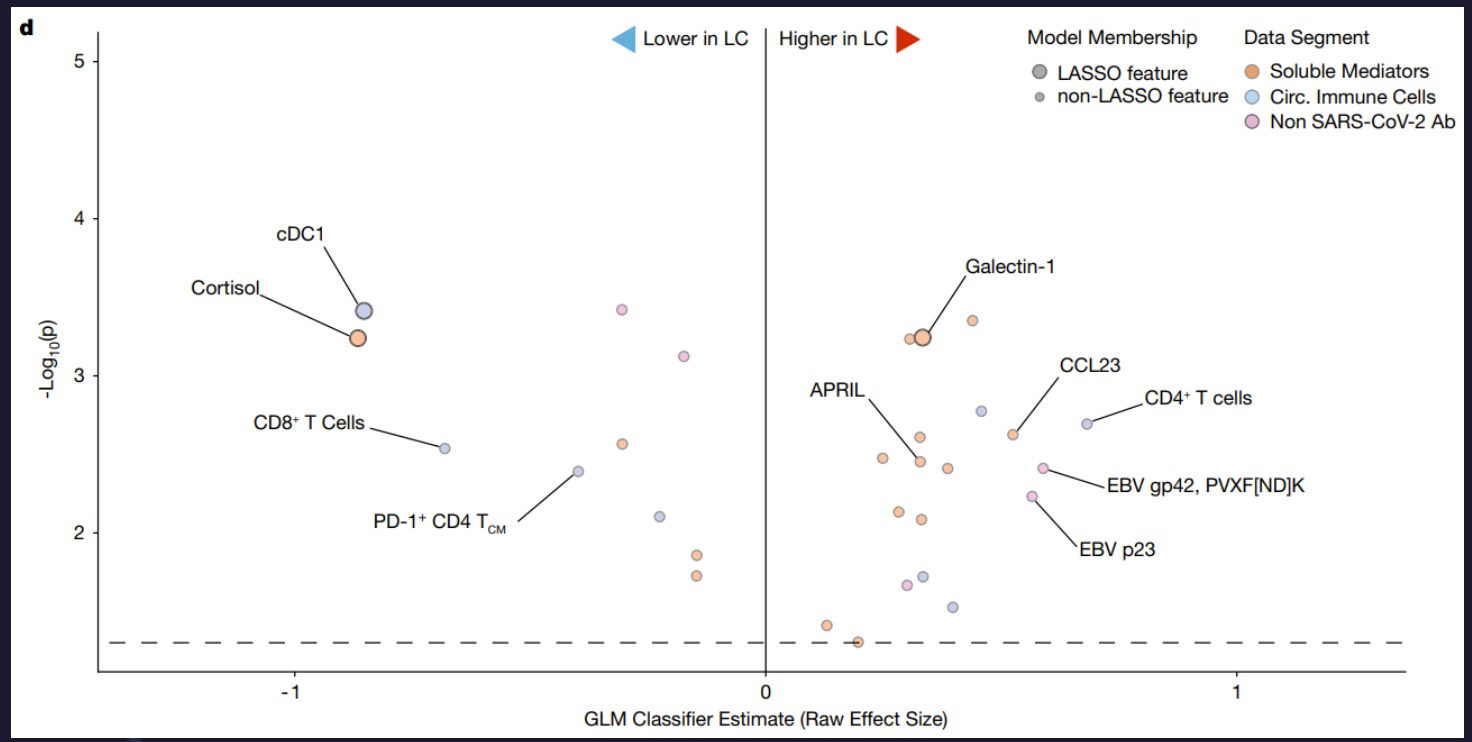


Klein 2023, PMID 37748514

nature › articles › article

Article | Open access | Published: 25 September 2023

# Distinguishing features of long COVID identified through immune profiling




- Yale-Mount Sinai LC centers study
- Cross-sectional study: 101 with Long COVID, (~1 year post onset) 42 healthy controls, 42 convalescent controls
- Multidimensional immune phenotyping and ML methods used to identify biological features associated with LC
- Marked differences were noted in circulating myeloid and lymphocyte populations relative to matched controls
- Evidence of exaggerated humoral responses directed against SARS-CoV-2 were found among participants with LC

- Higher antibody titers against non-SARS-CoV-2 viral pathogens, particularly EBV, observed in LC group
- Levels of soluble immune mediators and hormones varied; cortisol levels were lower in LC group
- HLA-DR genotype and "non-conventional monocytes" ($CD14^{low}CD16^{high}$) were highest in LC group

nature immunology

Letter

https://doi.org/10.1038/s41590-024-01778-0

# Large-scale phenotyping of patients with long COVID post-hospitalization reveals mechanistic subtypes of disease

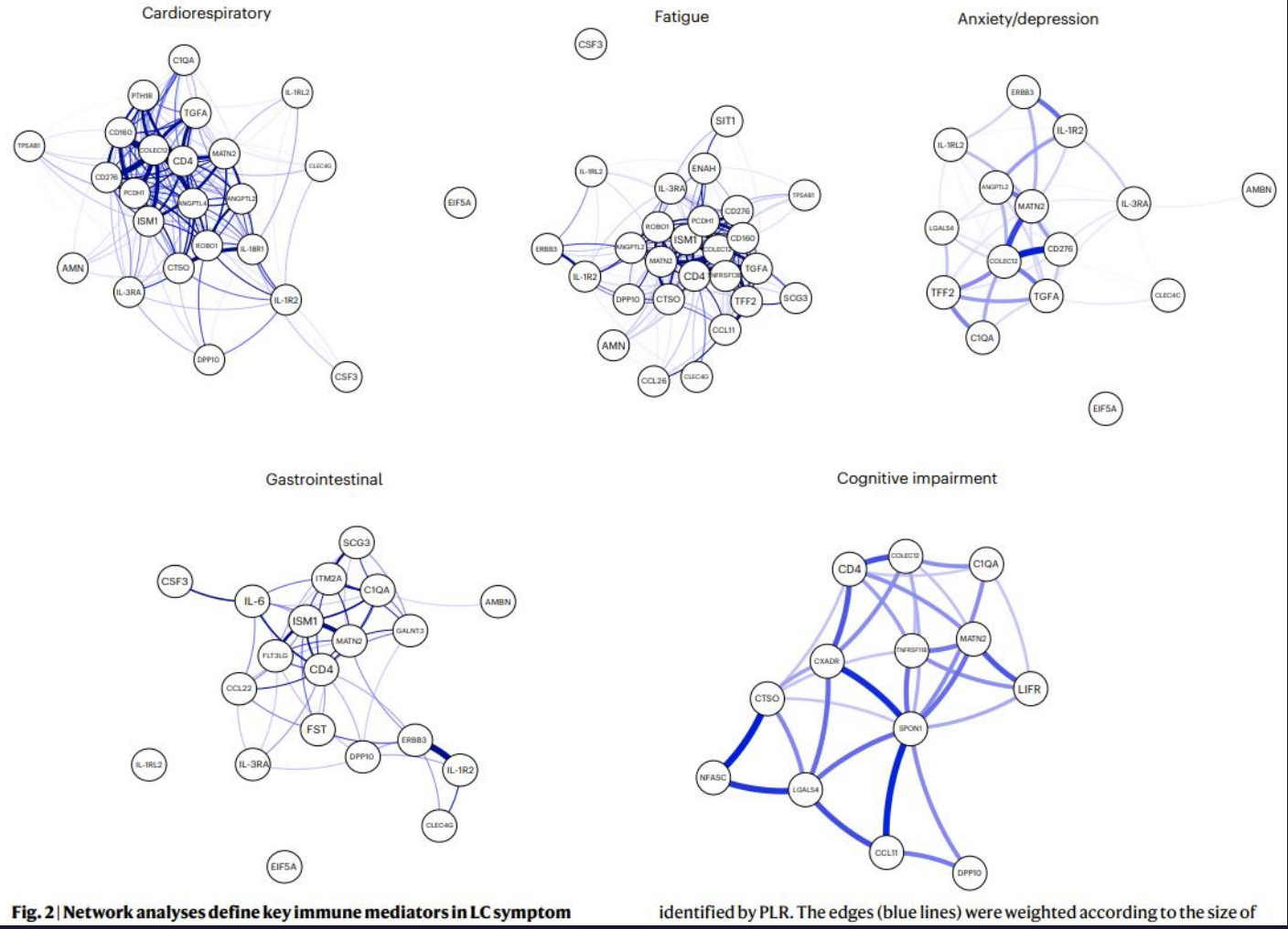


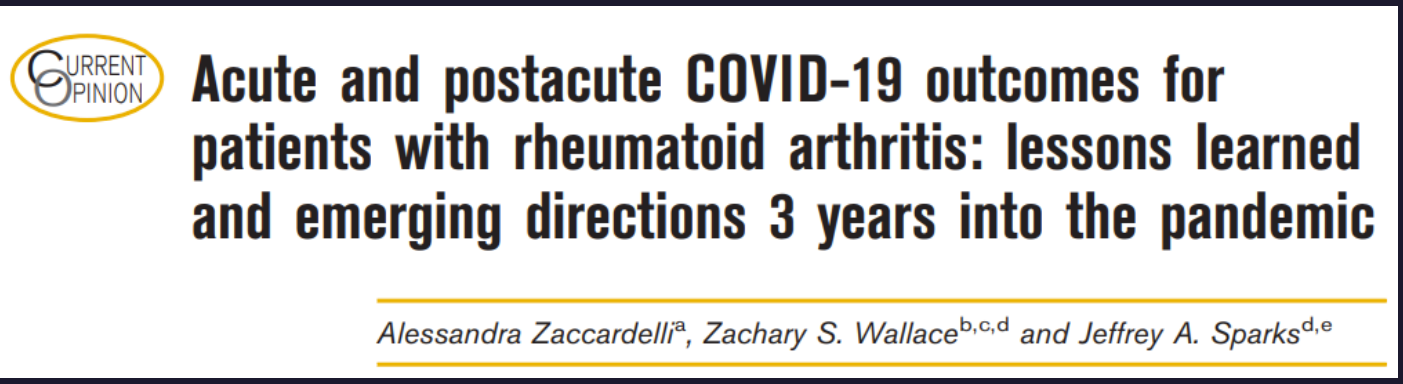

**Fig. 2 | Network analyses define key immune mediators in LC symptom** identified by PLR. The edges (blue lines) were weighted according to the size of

- UK PHOSP-COVID collaborative group.
- Subtypes of LC were associated with distinct inflammatory profiles.
- Used network analysis to map key immune mediators/markers to LC symptom groups.
- Elevated immune mediator levels most pronounced in older women with LC.
- Markers of myeloid inflammation and complement activation in the cardioresp, fatigue, anxiety/depression, cognitive and GI groups 6 months after hospitalization with COVID-19.

Liew 2024, PMID 38589621

# Post-COVID Reactive Arthritis?

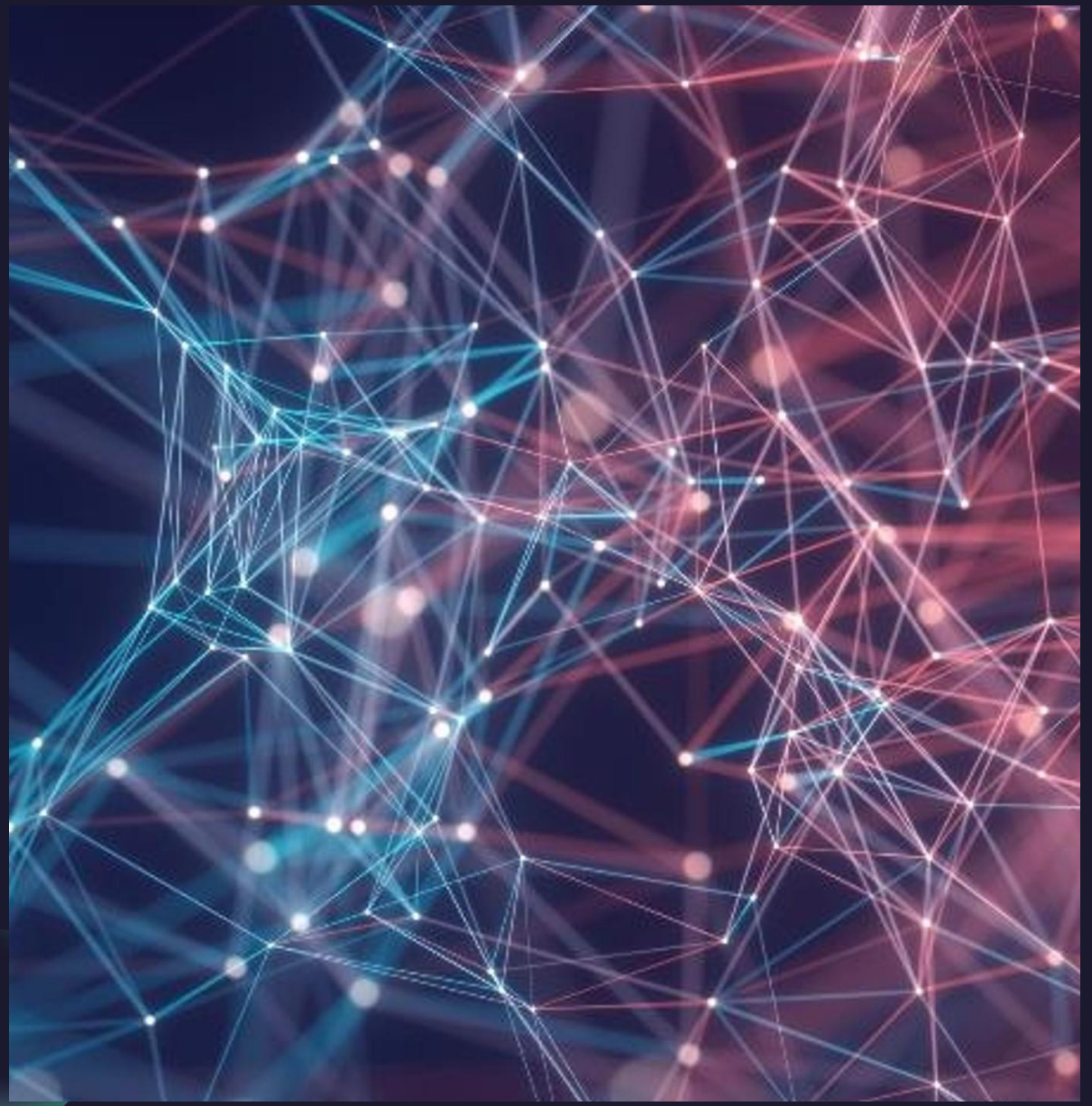
- "Can present at extremes of age, appears to affect both sexes equally and can have different presentations. Some present with small joint arthritis, others with SpA phenotype-either with peripheral or axial involvement, while a few have only tenosynovitis or dactylitis. The emergence of post-vaccination inflammatory arthritis hints at similar pathophysiology involved. There needs to be a global consensus on whether or not to include all such conditions under the umbrella of ReA." (Bekaryssova et al., 2022, PMID 35247132)
- Managed with NSAIDs, some received intra-articular steroids or oral steroid taper
- Definitions and data very uneven. One study in Egypt found 37/100 patients reported artihritic pain in patients 6 months post index infection, most commonly in ankle, knee, and wrist joints; associated with older age and smoking; patients with arthritis had higher ESR and CRP as well as *pre-illness* IL-6 levels. No significant association with ANA, anti-CCP, C3, C4. "Is it hyperinflammation or autoimmunity?" (Taha et al. 2021, PMID 35118946)




- Most studies early in the pandemic pooled patients with systemic autoimmune rheumatic diseases and on therapeutic immunosuppression due to limited sample size. Many of these studies found high risk of COVID-19 and severe outcomes, including hospitalization, hyperinflammation, mechanical ventilation, and death.
- Later studies with focus on RA found similar associations, while also identifying RA-specific factors such as immunosuppressive medications, disease activity/severity, and RA-ILD as risk factors for severe COVID-19.
- After vaccination, the risks for COVID-19 infection and severity were reduced for patients with RA, but a gap between the general population persisted. Some patients with RA remain susceptible to breakthrough infection after vaccination.
- Preexposure prophylaxis, effective treatments, and changes in viral variants have also contributed to improved COVID-19 outcomes among patients with RA throughout the pandemic.
- Emerging data suggest that patients with RA may be at risk for postacute sequelae of COVID-19 (PASC). Shared mechanisms include autoimmunity, hyperinflammation, hypercoagulability, and fibrosis.

Zaccardelli 2023, PMID 36752280

# Clinical Experience Discussion



# Resources

The Office of Long COVID Research and Practice (OLC) | HHS.gov

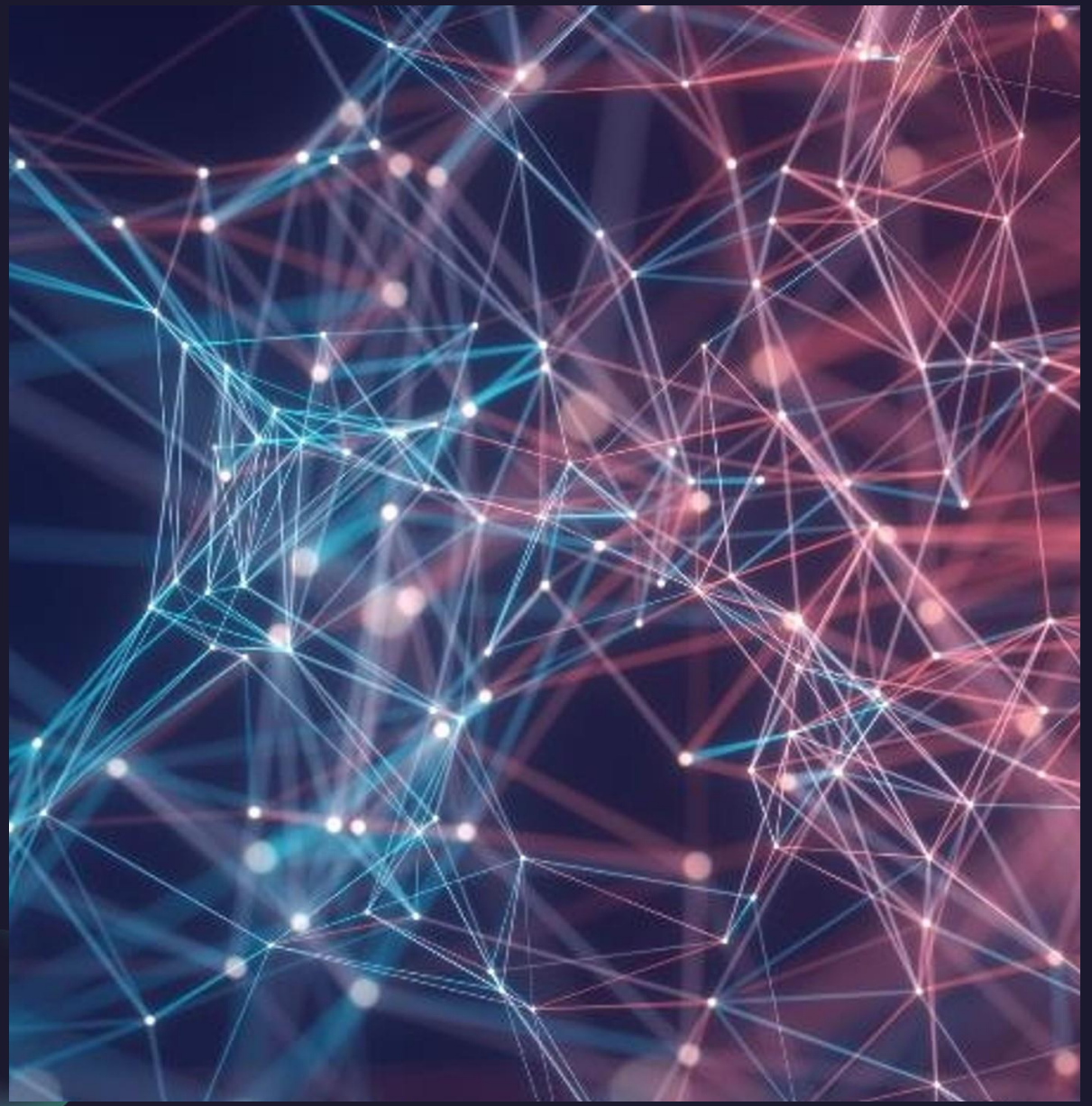
Home | ClinicalTrials.gov

Long COVID | NHLBI, NIH

Coronavirus Resources | U.S. Department of Labor (dol.gov)

Survivor Corps, Long COVID Alliance

Post-COVID Rehabilitation | UW Medicine



# Appreciation and Gratitude

Patients and staff of the GWU Medical Faculty Associates COVID Recovery Clinic (2020-2022)

Aileen Chang, MD, MSPH, Associate Professor, Department of Medicine, GWU SMHS

Adrienne Poon, MD, MPH, Associate Professor, Department of Medicine, GWU SMHS

Gary L. Simon, MD, PhD, Professor Emeritus, Division of Infectious Diseases, GWU SMHS